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Microsleep episodes in the borderland between wakefulness and sleep

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Microsleep episodes in the borderland between wakefulness and sleep

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Abstract

Study objectives: The wake-sleep transition zone represents a poorly defined borderland, containing e.g. microsleep episodes (MSEs) which are of potential relevance for diagnosis and may have consequences while driving. Yet, the scoring guidelines of the American Academy of Sleep Medicine (AASM) completely neglect it. We aimed to explore the borderland between wakefulness and sleep by developing the Bern continuous and high-resolution wake-sleep (BERN) criteria for visual scoring, focusing on MSEs visible in the electroencephalogram (EEG), as opposed to purely behaviour- or performance-defined MSEs.

Methods: Maintenance of Wakefulness Test (MWT) trials of 76 randomly selected patients were retrospectively scored according to both the AASM and the newly developed BERN scoring criteria. The visual scoring was compared with spectral analysis of the EEG. The quantitative EEG analysis enabled a reliable objectification of the visually scored MSEs. For less distinct episodes within the borderland, either ambiguous or no quantitative patterns were found.

Results: As expected, the latency to the first MSE was significantly shorter in comparison to the sleep latency, defined according to the AASM criteria. In certain cases, a large difference between the two latencies was observed, and a substantial number of MSEs occurred between the first MSE and sleep. Series of MSEs were more frequent in patients with shorter sleep latencies, while isolated MSEs were more frequent in patients who did not reach sleep.

Conclusion: The BERN criteria extend the AASM criteria and represent a valuable tool for in-depth analysis of the wake-sleep transition zone, particularly important in the MWT.

Keywords: Microsleep, wake-sleep transition zone, AASM scoring criteria, maintenance of wakefulness test, electroencephalography, sleepiness, sleep, wakefulness

Statement of significance

In this study, we developed the Bern continuous and high-resolution wake-sleep (BERN) scoring criteria as a first step towards closing an important gap of the scoring criteria established by the American Academy of Sleep Medicine, particularly required for classifying the wake-sleep transition zone. We were able to objectify our visual scoring criteria by comparison with a quantitative analysis of the electroencephalography. The application of the BERN scoring criteria led to new and promising insights into the borderland between wakefulness and sleep. A further refinement combined with automatic detection and inclusion of behaviour and performance measures could offer a powerful new tool for clinical sleep medicine and research, improving the differential diagnosis, and the assessment of treatment and fitness to drive.

Introduction

Preceding the detection of rapid eye movement (REM) sleep by Aserinsky & Kleitmann,¹ Loomis and colleagues proposed a sleep classification, consisting of wakefulness and four different sleep stages.²⁻⁴ The stage B1 was related to “drowsiness”, and the stage B2 to “sleep onset”. Compared with later sleep scoring classifications, this initial classification of the wake-sleep transition zone contained more details. In 1968, Rechtschaffen & Kales (R&K) established the first globally applied criteria for classifying the electroencephalography (EEG) into wakefulness, non-REM sleep stages (N1-4), and REM sleep.⁵ It was only in 2007, after almost 40 years, that the American Academy of Sleep Medicine (AASM) revised the criteria of R&K.⁶ Since then, the AASM has generally revised their criteria on a yearly basis with the latest revision (version 2.5) being published in April 2018.⁷ The AASM scoring criteria, and formerly the R&K criteria, represent the international standard for scoring sleep and wakefulness in the most important diagnostic sleep-wake tests, such as polysomnography (PSG), the Multiple Sleep Latency Test (MSLT), and the Maintenance of Wakefulness Test (MWT).⁸ In addition to the clinical use, the scoring criteria are widely used in clinical and basic sleep research.

Historically, EEGs were recorded on paper with a standard running speed of 10 mm/s, mostly with an epoch length being defined as 30 s, equivalent to a one-page EEG recording. Surprisingly, the defined length of 30 s has outlasted the digitalisation of EEG recordings and variations in computer screen size. Similarly, the clinical scoring criteria underwent few changes and still do not adequately address the wake-sleep transition zone, despite the technical advances and expanded knowledge on the process of falling asleep.⁹ In addition to the absence of an intermediate stage between wakefulness and N1, the low temporal resolution (30 s) does not take the rapid fluctuations between different stages into consideration. This is of particular importance in the MWT, during which individuals are instructed to stay awake despite their potentially excessive sleepiness, thus, prolonging the time spent within the wake-sleep transition zone. Although limited, normative data are available for scoring epochs shorter than 30 s in the MWT, i.e. a minimum of 10 s resolution.^{10,11} The rapid fluctuations between wakefulness and sleep characterise the typical instability in the wake-sleep transition zone and may result in so-called microsleeps or microsleep episodes (MSEs). Wake-sleep fluctuations can persist over protracted time periods, particularly during daily performance tasks such as driving, and increase the chance for MSEs to occur, potentially resulting in fatal accidents. In contrast to the MWT and performance tasks, a rather rapid transition from wakefulness to

deeper sleep stages can be observed in PSG or the MSLT, during which individuals are allowed to fall sleep.

Unfortunately, there is no generally accepted definition regarding the true meaning of a MSE. The definition depends mainly on the type of the recorded signal and can be classified into the following three categories^{12,13}: (1) EEG or other neurophysiological parameters (visual and automatic), (2) eye, eyelid, or face/body behaviour, and (3) psychomotor performance measures. Several parameters from any type of recording can be utilised alone or in combination.

In clinical sleep medicine, MSEs are predominantly defined by short lasting EEG patterns resembling sleep (mainly N1). However, it is important to be aware that signs and symptoms, as well as performance lapses can occur before the appearance of a clear-cut sleep-like EEG pattern in the superficial EEG.^{12,14,15} In our understanding, sleepiness is a condition that precedes sleep and reflects increased sleep pressure, which, depending on the task and the level of sleepiness, cannot always be perceived subjectively.¹⁴ While sleepiness and drowsiness are often used synonymously, in our view, the latter represents a variant of sleepiness during which MSEs are not necessarily visible in the EEG. Drowsiness is frequently accompanied by physiological measures such as eyelid drooping, rolling eye movements, slowing in heart rate or respiration, and performance impairments.^{12,16} The discrepancy between the observation of behavioural changes in the absence of a correlating pattern in the surface EEG can be explained by local sleep starting in subcortical brain structures that is not visible in the surface EEG before spreading to the cortex.^{17,18} However, higher levels of sleepiness result in EEG patterns that can also be objectified in superficial EEG while behavioural changes are simultaneously observable.^{19,20} Accordingly, a differentiation of “EEG-defined MSEs”, “behaviour-defined MSEs”, and “performance-defined MSEs” is primarily dependent on the assessment method but does not necessarily reflect the underlying physiological processes. In clinical sleep medicine and research, the EEG still represents the method of choice for defining MSEs. Behavioural or performance measurement tools are often not available. However, combining the EEG with face videography can improve the reliable identification of MSEs in the MWT.²¹ Therefore, it has long been standard practice to record both during the MWT in the Sleep-Wake-Epilepsy-Centre of the Bern University Hospital.

The present study focused on the wake-sleep transition zone, which ranges from full wakefulness through the first signs of sleepiness to severe sleepiness and sleep, the latter defined according to the AASM criteria. Among all tests available in a clinical environment,

the MWT best resembles a passive real-life condition (e.g. surveillance task) in which MSEs are of particular relevance. Furthermore, the sleep latency in the MWT not only correlates with driving performance,²² but this correlation is stronger than the one of sleep latency in the MSLT and driving performance,²³ although this is without taking MSEs into account. Therefore, we aimed to identify MSEs with a high temporal resolution and great specificity in the MWT.

The primary aim of this study was to define practicable visual EEG scoring criteria for the wake-sleep transition zone, taking a first step towards the closure of the gap in the AASM scoring criteria. The first objective was to formulate the Bern continuous and high-resolution wake-sleep (BERN) criteria for visually scoring MSEs and similar less clearly defined EEG patterns in the MWT with a high temporal resolution (i.e. minimal duration of one second). The second objective was to compare the visual scoring of MSEs according to the newly developed BERN criteria with quantitative EEG and electrooculography (EOG) analyses.

The secondary aim of this study was to further analyse and characterise the borderland between wakefulness and sleep. The first objective of the secondary aim was to descriptively analyse MSEs and investigate their impact on the ‘sleep latency’ by comparison of the latency to the first MSE with the latency to sleep. The second objective was to analyse the temporal distribution and dynamics of MSEs.

Methods

Study population

From the clinical database of the Sleep-Wake-Epilepsy-Centre of the Bern University Hospital, MWT recordings of 76 patients (mean age 45.6 years, range: 18 – 81.3 years, 50 males) were randomly selected in retrospect. The final diagnosis was of no interest to the present study but excessive daytime sleepiness (EDS) had to be suspected and consequently, patients had to have undergone an MWT. The study was conducted according to the Declaration of Helsinki, Swiss Law, and the ethical approval of the local ethics committee (KEK-Nr. 308/15). Patient data were included based on a general consent of patients, signed when entering the Bern University Hospital.

Procedure, assessment, and material

The MWT consists of four trials that are conducted over the course of a day, with two trials before and two trials after lunch, and a minimum break of 2h between trials. In this study, we

aimed for a wide spectrum of patients with differing degrees of sleepiness allowing an inter-individual rather than an intra-individual comparison. Hence, we scored only one MWT trial per patient (the third, recorded at ~ 3 pm), instead of scoring all four MWT trials of fewer patients. We chose the third MWT trial as we expected most MSEs to occur in this trial, scheduled during the well-known post-lunch dip of vigilance.

During the MWT, patients had to sit on a chair in a semi-darkened room (0.1 Lux at corneal level) for 40 min and were instructed to stay awake for as long as possible.²⁴ Standard EEG (O1-M2, O2-M1, C3-M2, C4-M1, CZ-M1, F7-M2, F8-M1, sampling rate 200 Hz, 0.3 Hz high-pass and 70 Hz low-pass filter (35 Hz for display), 50 Hz powerline notch filter, impedance below 5 k Ω at the beginning of a recording), EOG, submental electromyography, electrocardiography, respiratory flow, and face videography (including audio) were simultaneously recorded (RemLogic™; Embla Systems LLC). The laboratory technicians were instructed to terminate each trial after 40 min or after online identification of three consecutive epochs of N1 or one epoch of any other sleep stage, defined according to the AASM scoring criteria.⁷

Bern continuous and high-resolution wake-sleep (BERN) scoring criteria

We developed the BERN criteria for scoring MSEs of 1 to 15 s duration based on the visual analysis of the occipital EEG leads, face videography (eyelid position), and the EOG (e.g. slow eye movements). We classified the wake-sleep transition zone primarily into wakefulness and MSEs, and the additional categories of microsleep episode candidates (MSEc) and episodes of drowsiness (ED; Table 1). We defined wakefulness according to the AASM scoring criteria with the exception that it could be of any duration longer than 1 s. MSEs are similar to N1 according to the AASM criteria, with the additional criterion of $\geq 80\%$ eyelid closure in the face videography, which was observed visually. Although behaviour-defined, performance-defined MSEs, and even EEG-defined MSEs may appear with open eyes, we included the eyelid position as short bouts of wakefulness and sleep are more difficult to distinguish in the EEG when the eyes are open, in the absence of the Berger effect (blockage of alpha).²⁵ Accordingly, our current definition for MSEs is rather conservative and specific while our definition of MSEc, not taking the eyelid position into consideration, is more sensitive. MSEc are used for those episodes which do not fulfil all the criteria of MSEs. The category of ED is applicable for episodes that cannot be clearly defined, as they contain rapidly fluctuating (i.e. below one second) aspects of wakefulness, MSEs, and MSEc.

Scoring

The recording was visually scored from the beginning of the test (lights off) until the MWT trial was terminated. Two scoring criteria were applied: the AASM criteria and the newly developed BERN criteria, the latter restricted to the occipital leads. By definition, the recording was scored in stepwise consecutive epochs of 30 s when applying the AASM criteria, which was scored by clinicians during clinical routine. When applying the BERN criteria, the EEG was scored continuously in order to identify MSEs (definition available in Table 1) with a minimum duration of one second. The latency from lights off to the first epoch of sleep was defined as AASM sleep latency (AASM-SL) and set to 40 min if no sleep occurred. Similarly, the latency from lights off to the onset of the first MSE was defined as MSE-L. The analyses in this study focused on the wake-sleep transition zone until the occurrence of sleep.

A substantial proportion of scoring was conducted by AHG after being trained by experienced scorers (DRS and JM). In around 2/3 of the trials, the final scoring was verified by the experienced scorers and differences were resolved by discussion.

Inter-scorer reliability

Of the 76 patients, five patients with many events (MSEs, MSEc, ED) scored by AHG were randomly selected for an independent second scoring by DRS, blind to the first scoring. In addition, the recording was not scored until sleep onset only but until the end of the test (lights on), in order to score as many events as possible for the calculation of the inter-scorer reliability. Inter-scorer reliability was assessed by the Cohen's kappa coefficient as a robust measure.²⁶ Further details regarding the calculations are described in Skorucak et al.²⁷

Quantitative analysis

Spectral analysis was performed with a parametric approach (autoregressive model of order 16; Burg method²⁸) on the two occipital EEG derivations. A one-second segment was moved through the data in steps of 200 ms and the spectra were represented as a spectrogram (Figure 1). This method allowed high temporal resolution and quantification of EEG frequencies such as alpha or theta activity. The spectra provided the basis for deriving quantitative features (Figure 2) to characterise the MSE (more detailed description in the accompanying article²⁷). The quantitative analysis was performed using MATLAB (R2018a, The MathWorks Inc., Natick, Massachusetts, United States).

Comparison of the BERN scoring criteria with quantitative features

Visual EEG scoring remains largely subjective. Thus, quantitative EEG and EOG analysis allows framing the subjective scoring into an objective context (Figure 1). In the MWT, wakefulness represents the initial and default state, which is why we were not interested in quantitative EEG features of wakefulness as such. However, we were interested in the features present at the transition from wakefulness to another category and vice versa, eventually leading to the definition of the categories of the BERN scoring criteria. We quantitatively characterised MSEs with the following seven features derived from the occipital EEG spectrogram and the EOG: 1. power in the delta (0.8 – 4 Hz), 2. theta (4 – 8 Hz), 3. alpha (8 – 12 Hz), and 4. beta (12 – 26 Hz) bands, 5. the ratio of theta/(alpha+beta) activity, 6. the median EEG frequency in the 0.8 - 26 Hz range, and 7. the occurrence of eye movements (ratio of delta activity of the EOG and delta activity of the occipital EEG) (Figure 2). As delta activity originating from the brain is present in both the EOG and EEG leads, and eye movements mainly cause delta activity in the EOG, the ratio of delta activity of the EOG and of the EEG uncovers eye movements. This eye movement quantification is only an approximate measure and does not allow the differentiation of different kinds of eye movements, or eye closure. Therefore, eye closure was not a feature of the quantitative analysis. At the transition from wakefulness to a MSE, alpha activity diminished concordant with a drop in beta activity, followed by the appearance of theta activity (Figure 1). In addition, we frequently found an increase in the ratio of theta activity divided by the sum of alpha and beta activity (Figure 2, T/AB), a slowing of the EEG as indicated by a reduction in the median frequency (Figure 2, med. f.), and a lack of eye movements (Figure 2, eye m.). We did not always observe a clear increase in theta activity. The quantitative EEG features relevant for MSEs were also partially relevant for MSEc (Figure 1), as MSEc by definition share some aspects with MSEs. No clear patterns could be identified for ED.

Statistical analysis

Statistical analyses were performed using Stata (StataCorp. 2017, Stata Statistical Software: Release 15.1. College Station, TX: StataCorp LLC). Pearson's coefficient is reported for correlation and the Wilcoxon Signed Rank Test was used for comparisons, all with $p < 0.05$ (two-tailed) as the level for statistical significance.

Results

Inter-scorer reliability of the BERN scoring criteria

On a theoretical spectrum ranging from full wakefulness to deep sleep, the defined categories of wakefulness, MSEc, and MSEs could be ranked in this order while the category of ED contains features of all of these. However, direct transitions from each category into one of the other categories may be possible. This assumption would imply that wakefulness and MSEs should be most distant from each other on the wake-sleep spectrum and therefore the easiest to differentiate visually, while ED should be the most difficult to differentiate. In line with this, the inter-scorer reliability calculations (Table S1) resulted in substantial identification of MSEs and wakefulness ($\kappa = 0.75 \pm 0.08$), slight identification of MSEC and wakefulness ($\kappa = 0.19 \pm 0.04$), and slight identification of ED and wakefulness ($\kappa = 0.07 \pm 0.02$) according to Landis and Koch.²⁹ The scoring by the two experts of all five patients is illustrated in Figure S1.

Comparison of the BERN with the traditional AASM scoring criteria

Of the 76 patients analysed, 30 patients (39%) did not reach sleep and had no MSEs, however, both MSEC and ED occurred in four, MSEC without ED in one, and ED without MSEC in four out of these 30 patients. Thirty-nine patients (51%) reached sleep, but only four of them without any preceding MSE (AASM-SL: median 13.7 s, IQR 9.9 – 20.3 s) while MSEC and ED were observed in these four patients. In the other 35 out of the 39 patients, sleep was always preceded by at least one MSE (Figure 3). In the seven remaining patients, MSEs were scored, even though the patients did not reach sleep, amounting to 42 patients (55%) with MSEs. Among these 42 patients, MSEC were scored in 40 and ED were scored in 37.

The relative cumulative MSE duration (in %; Figure 3b) for the interval between lights off and sleep onset was 11.3% (median, IQR 3.9 – 19.5%) and the relative cumulative duration of MSEs, MSEC, and ED altogether was 16.57% (median, IQR 8.6 – 30.7%). As the borderland between wakefulness and sleep was largely characterised by MSEs, and since the inter-scorer reliability and the quantitative analyses revealed the best results for MSEs, the subsequent results focus on the comparison between MSEs and sleep only. However, the complexity of MSEC and ED should be investigated in more detail in future, as these conditions might also be accompanied by reduced performance levels.

The median duration of MSEs per patient ranged from 1.1 to 12.5 s, the minimal duration from 1 to 12.5 s (median 1.7 s, IQR 1.1 – 2.3 s), and the maximum duration from 1.1 to 20.7 s (median 6 s, IQR 3.9 – 10.1 s) (Figure 4a-b). Over time, the MSE duration remained very heterogeneous, not necessarily increasing with time after lights off. The cumulative MSE duration per patient ranged from 1.1 s to 190.3 s (Figure 4c). The MSE-L was significantly shorter than the AASM-SL, and as expected, both showed a strong correlation with each other after excluding those seven patients with MSE(s) but no sleep, i.e. AASM-SL of 40 min (Table 2, Figure 5). The difference between the first MSE and sleep onset ranged from 0.05 to 33.85 min (Table 2, Figure 3). On average, sleep occurred six minutes after the occurrence of the first MSE (Figure 5, Table 2)

Of patients which exhibited MSEs, almost one third (28.6%) experienced only one MSE, while the total number of MSEs scored per patient ranged up to 31 (Table 2, Figure 4d). The frequency distribution of the MSE-L and AASM-SL in 5-min intervals (Figure 6a) illustrates that the majority of MSEs occurred in the first 25 min. In order to compare the difference between the BERN and the AASM scoring criteria regarding the first signs of sleepiness or sleep, we used a Kaplan-Meier estimator (Figure 6b). Within the first five minutes of the MWT, at least one MSE occurred in about 12% of patients and sleep in about 5% of patients, resulting in a seven percentage point difference. After seven minutes, this difference increased to 10-15 percentage points and remained stable until 15 min. From 15-28 min, the difference doubled and decreased again thereafter to 10-15 percentage points, also evident in the discrepancies between MSE-L and AASM-SL in the intervals 15-20 and 25-30 (Figure 6a).

Independent of the MSE-L, sleep occurred within four minutes following the first MSE in 50% of the patients (20/40), and within 10 min following the first MSE in a total of 80% (32/40; excl. the two patients with MSEs (2/42) but no sleep within the 40 min; Figure 3b). In 89% of the patients that did not reach sleep within 10 min following the first MSE (8/9), no second MSE occurred within four minutes following the first MSE. Moreover, five out of these eight patients completed the MWT trial without reaching sleep (three of them without even a second MSE). Consequently, if no second MSE occurred within four minutes after the first MSE and no sleep occurred within the 10 min following the first MSE, it seems likely that a patient will complete the MWT trial without reaching sleep. In addition, the interval between the first MSE and sleep correlated with the corresponding cumulative MSE duration (in %) of this time window ($r = 0.6970$, $p < 0.0001$, $n = 35$). Therefore, patients with a shorter interval between the first MSE and sleep spent a greater relative amount of this time period within MSEs.

The borderland between wakefulness and sleep

With the exception of three patients, sleep was preceded by at least one but in the majority by two or more MSEs (Figures 3, 4d). As we observed that most patients had MSEs both in series and in isolation but those patients that did not reach sleep mainly exhibited isolated MSEs (Figure 3a), the temporal relationship between MSEs is of interest. MSE series could be an important indicator of more severe sleepiness or lower compensation capacities in comparison to isolated MSEs. In addition, a better understanding of the distribution of MSEs in the time domain could be of high relevance for the prediction of longer MSEs in future. The distribution analysis of the inter-MSE intervals between the first MSE and sleep suggested that most MSEs are part of a MSE series (Figure 4e). However, the heterogeneous number of MSEs among patients introduced bias into these findings.

Discussion

This study introduces the Bern continuous and high-resolution wake-sleep (BERN) scoring criteria for the visual scoring of the wake-sleep transition zone in the MWT. The quantitative EEG and EOG analysis enabled an objectification of the visually scored MSEs. The quantitative MSE features were also partially relevant for MSEc but did not allow objectification of ED. Hence, only MSEs were included in the subsequent analysis, which showed the expected findings that the MSE-L is significantly shorter than the AASM-SL and that patients rarely reached sleep without any preceding MSE. Rather unexpected was how early and frequently MSEs occurred prior to the much later onset of sleep in some patients.

In the last 10 to 20 years, the understanding of wakefulness and sleep has changed significantly. In contrast to the traditional epoch-by-epoch method of sleep scoring, there have been several studies addressing shorter time scales.^{14,30-36} The minimal duration of MSEs reflected in the EEG was generally defined as three seconds, characterised by a replacement of attenuated alpha with theta activity, or less precisely by e.g. “short-lasting burst of typical stage 1 sleep”.^{14,30-36} By using such definitions, a great proportion of MSEs might be missed, as approximately 40% of MSEs in our study lasted between one and three seconds. On the other hand, the restriction to a minimal MSE duration of three seconds certainly allowed a more specific detection and the inclusion of shorter MSEs may bear the risk of false positive scoring. However, these previous studies did not compare the visually scored MSEs with a quantitative EEG analysis. Our quantitative analysis allowed a more precise characterisation of MSEs with mainly a

diminution of alpha activity concordant with a drop in beta activity, followed by the appearance of theta activity, and thus an increase in the theta/(alpha+beta) ratio (Figure 2, T/AB).

There are several reasons why the scoring of MSEs has not yet been implemented in the standard clinical routine: the absence of standardised and clearly defined scoring criteria, the partial lack of training, and time constraints as the accurate scoring of MSEs is substantially more time consuming than the scoring of 30-s epochs. In addition, the meaning of MSEs regarding the severity of sleepiness, with respect to the precise diagnosis of the underlying disorder, and their relevance for the ability to drive is still unknown. The relationship between MSEs defined according to the EEG, behaviour, and performance needs to be further investigated. Behavioural changes and performance lapses may not always be accompanied by detectable changes in the EEG and vice versa, and the first MSE may not necessarily lead to a traffic accident. More likely, and independent of their definition, multiple MSEs will often precede an accident,³⁷ which increases the chances of detecting at least one MSE prior to a crash independent of the assessment method.

The proposed BERN scoring criteria are a new attempt to establish practicable and standardised scoring criteria for the wake-sleep transition zone not addressed by the AASM. The BERN criteria improve the visual scoring with respect to shorter time scales but also characterise MSEs in more detail. With a kappa of 0.75 for MSEs and wakefulness, they reached a similar or improved inter-scorer reliability than published for N1 which reaches an agreement of around 60%^{38,39} or a kappa of <0.5 ^{40,41} respectively. In contrast to MSEs, MSec and ED are still far from being practically applicable, even though ED and wakefulness, which are the most difficult to differentiate, were still scored with slight agreement. Consequently, not only the scoring but also the training of scorers takes a long time and the subjectivity of the scoring remains high. Therefore, it seems reasonable to complement the visual EEG scoring by applying machine learning with the aim to compensate for the lack of training, improve the speed of analysis, and reduce the time required for the visual EEG analysis.²⁷ In future, algorithms may even completely replace visual scoring, or at least significantly reduce the workload in semi-automatic MSE scoring. As the visual scoring currently remains time consuming, we did not as yet cover topographical aspects in the BERN scoring criteria, although we have observed local MSEs in other EEG leads. Several studies have demonstrated the simultaneous co-existence of different states in the brain, i.e. local sleep and local wakefulness, or local differences of sleep.^{17,42-45} It was also shown that alpha activity moved from the posterior to the anterior areas of the brain during hypnagogic periods.⁴⁶ Consequently,

topographical aspects should be considered in the future, ideally explored initially through simultaneous recording at the surface of the scalp and intracranially.

Besides the methodological advances, a better understanding of the impact and meaning of MSEs in active and passive conditions is needed. A recent study showed that over several days following sleep restriction healthy individuals felt refreshed after the recovery night but EEG-defined MSEs were still present, lasting 3–14 s with alpha being replaced by theta activity.³⁶ The authors concluded that MSEs are a sensitive objective marker for daytime sleepiness. The discrepancy between subjective sleepiness on the one hand, and objective sleepiness as measured by MSEs on the other, has been reported in previous studies.^{14,47}

The identification of an accurate biomarker for sleepiness is of high relevance as methods for reliably objectifying sleepiness are urgently sought.⁴⁸ The present findings also support previous studies showing that inclusion of MSEs in the MSLT, the clinical gold standard to quantify sleepiness (i.e. sleep propensity)^{49,50}, improved the sensitivity of the EDS assessment.^{16,32}

The present study revealed a positive correlation between MSE-L and AASM-SL, and the occurrence of the first MSE was followed by sleep within four minutes in 50%, and within 10 min in a total of 80% of the patients with at least one MSE prior to sleep. Conversely, if no second MSE occurred within four minutes, there was an 89% chance that no sleep occurred in the 10 min following the first MSE. Nevertheless, the moment of the first MSE cannot yet be predicted.

MSEs predominantly occurred in series (short inter-MSE intervals) but also in isolation (long inter-MSE intervals). Isolated MSEs mainly occurred in patients who did not reach sleep. Therefore, MSEs might not only be a biomarker for sleepiness but their temporal distribution might also be an indicator of the severity of sleepiness. The MWT is still the preferred test for assessing compensational mechanisms to counteract sleepiness as milder forms of sleepiness are more readily revealed in such a passive and non-stimulating environment in comparison to a more activated state, e.g. in a driving simulator.^{22,50} However, an individual's motivation to maintain wakefulness when undergoing the MWT significantly affects sleep latency, while the latency cannot be voluntarily decreased in the MSLT.^{51,52} It could be speculated that similar to the sleep latency in the MSLT, the MSE-L in the MWT could be an indicator of the underlying sleepiness, which might be less affected by motivation and compensational mechanisms than the sleep latency itself, similar to the results of Bougard et al.³⁶ However, the interval between the first MSE and sleep onset with the corresponding number of MSEs and their temporal

distribution, and the cumulative MSE duration could be an indicator of motivational and compensational mechanisms. In the present study, a shorter interval between the first MSE and sleep was often associated with the occurrence of a MSE series and a longer cumulative MSE duration (in %) in this interval, which could point to rather severe sleepiness. In contrast, a longer interval between the first MSE and sleep in combination with few isolated MSEs may indicate intact compensational mechanisms but a limited motivation to counteract sleepiness. Nevertheless, further data and analyses are needed for confirmation. This would be of particular clinical relevance, as it could potentially allow the identification of patterns that are specific for certain disorders but also patterns that could more adequately reflect the success of treatment.

Conclusions, limitations, and outlook

This study provided the first continuous and high-resolution scoring criteria for MSEs, which were confirmed by quantitative EEG analysis. We observed that two thirds of the MSEs lasted between one and five seconds, confirming the need for a definition based on short time periods. MSEs occurred significantly earlier than sleep, resulting in sometimes much shorter latencies in comparison to the AASM-SL. According to our data, MSEs might also predict the AASM-SL to a certain degree. However, a large inter-patient variability exists, and a limitation of the study is certainly that we did not consider either the diagnosis, and therefore the cause of EDS, or the intake of drugs. Centrally active drugs may influence the EEG and different types of disorders may potentially affect the relation between MSE-L and AASM-SL, due to disease related levels of sleepiness and compensation capacities.

Nevertheless, the BERN scoring criteria provide a valuable tool to better explore the borderland between wakefulness and sleep. They should help to classify MSEs as an expression of EDS independent of the diagnosis and treatment. Therefore, we did not yet perform any sub-analyses with respect to the diagnosis since this was out of the scope of the present study. As this study included patients who were referred to the Sleep-Wake-Epilepsy-Centre because of EDS, independent of the final diagnosis, the present findings regarding the occurrence and duration of MSEs before sleep onset are not directly transferrable to specific patient groups or to the general population. In the future, the analysis of MSEs could be of important diagnostic value for a more reliable differentiation between ambiguous disorders of EDS (including narcolepsy, idiopathic hypersomnia and non-organic hypersomnia) and chronic fatigue.

Another limitation is that we only analysed the third out of four MWT trials. Extending the analysis to all MWT trials might have further improved the understanding of our results. It may have solved the question of whether the different distributions of MSEs in the borderland between wakefulness and sleep are trait- or state dependent, and it would have allowed the investigation of circadian or time-of-day aspects. However, it was not feasible to carry out this level of visual scoring. Consequently, the number of patients was relatively small for the analysis of subgroups. For future research, a larger number of patients and MWT trials per patient, and therefore more MSEs could be scored automatically.²⁷ The BERN scoring criteria build the foundation for such an automated scoring of MSEs, which potentially makes the scoring in the wake-sleep transition zone not only more accurate and standardised, as the visual scoring requires training and will remain subjective, but also more efficient.

Future research should also explore the occurrence of MSEs in the spatial domain, e.g. including frontal and central EEG leads. In addition, an automatic analysis of the eyelid position could be developed, and the BERN scoring criteria could be tested in PSG and MSLT, without including the eyelid position. Based on the outcome, the BERN scoring criteria may have to be revised and/or extended.

The BERN scoring criteria were developed and are currently applicable to identify EEG-defined MSEs in the MWT. However, the borderland between wakefulness and sleep needs to be further investigated, including also behaviour- and performance-defined MSEs, as this could lead to significant improvements in the differential diagnosis of disorders and a more sensitive assessment of treatment and fitness to drive.

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Disclosure statement

Financial Disclosure: none.

Non-financial Disclosure: none.

List of abbreviations

AASM	American Academy of Sleep Medicine
AASM-SL	Latency from lights off to the first epoch of sleep (AASM criteria)
BERN	Bern continuous and high-resolution wake-sleep (scoring criteria)
ED	Episode(s) of drowsiness
EDS	Excessive daytime sleepiness
EEG	Electroencephalography
EOG	Electrooculography
MSE(s)	Microsleep episode(s)
MSE-L	Latency from lights off to the first microsleep episode
MSEc	Microsleep episode candidate(s)
MSLT	Multiple Sleep Latency Test
MWT	Maintenance of Wakefulness Test
N1-4	Non-rapid eye movement sleep stages 1-4
PSG	Polysomnography
R&K	Rechtschaffen and Kales
REM	Rapid eye movement

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Figures

Figure 1. Example of a microsleep episode candidate (MSEc, delineated by blue lines) and a microsleep episode (MSE, delineated by red lines). Electrooculography (E1/E2), electroencephalography with derivations O1-M2 and O2-M1 and the corresponding spectrograms (-20 dB  25 dB; 0 dB = $1 \mu\text{V}^2/\text{Hz}$) are illustrated. During the MSEc, alpha partially disappeared in the second half and some theta activity emerged. During the MSE, alpha disappeared and theta activity emerged, while a simultaneous drop in beta (dark blue areas) was observed. After the MSE, alpha activity was re-established. Rolling eye movements were present during both the MSEc and the MSE.

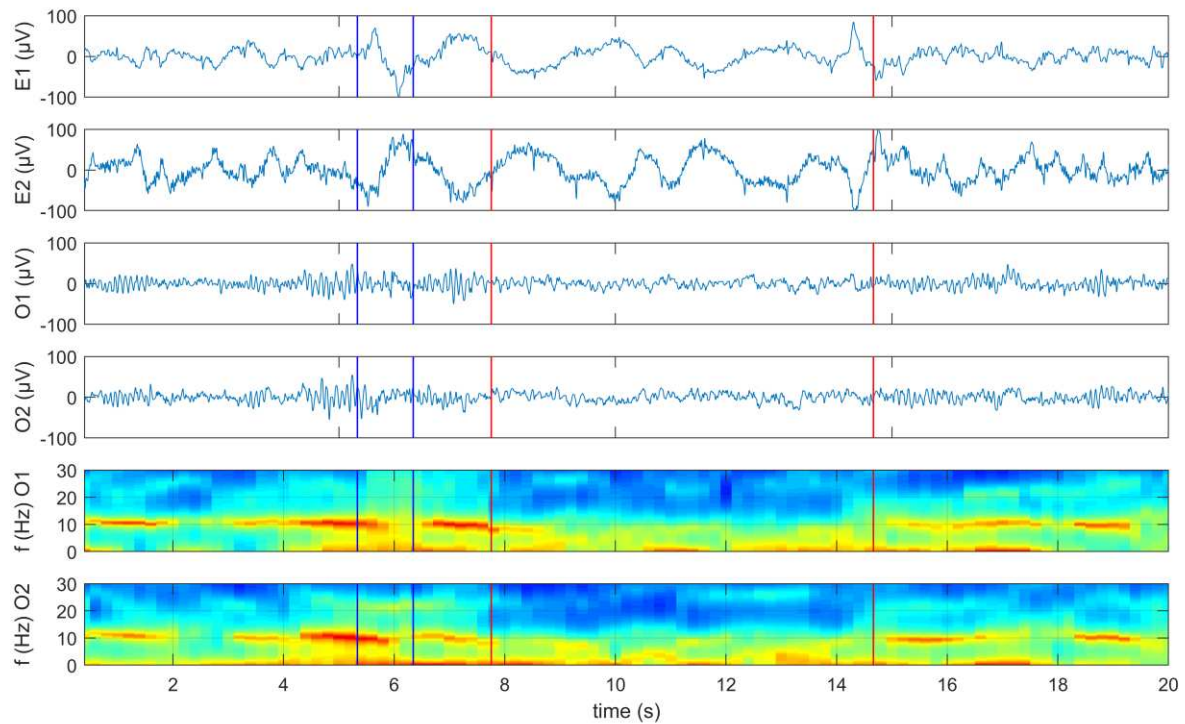


Figure 2. Quantitative features with microsleep episodes (MSEs) highlighted in red are illustrated: power in the delta (0.8 – 4 Hz), theta (4 – 8 Hz), alpha (8 – 12 Hz), beta (12 – 26 Hz) frequency bands, T/AB = ratio theta/(alpha+beta), eye movements (eyes, delta activity of the electrooculography divided by delta activity of O2-M1), and median electroencephalographic frequency (0.8 – 26 Hz range). Derivation O2-M1 was analysed (120 s). Power in the delta, alpha, theta, and beta range was smoothed by a 1-s moving median filter.

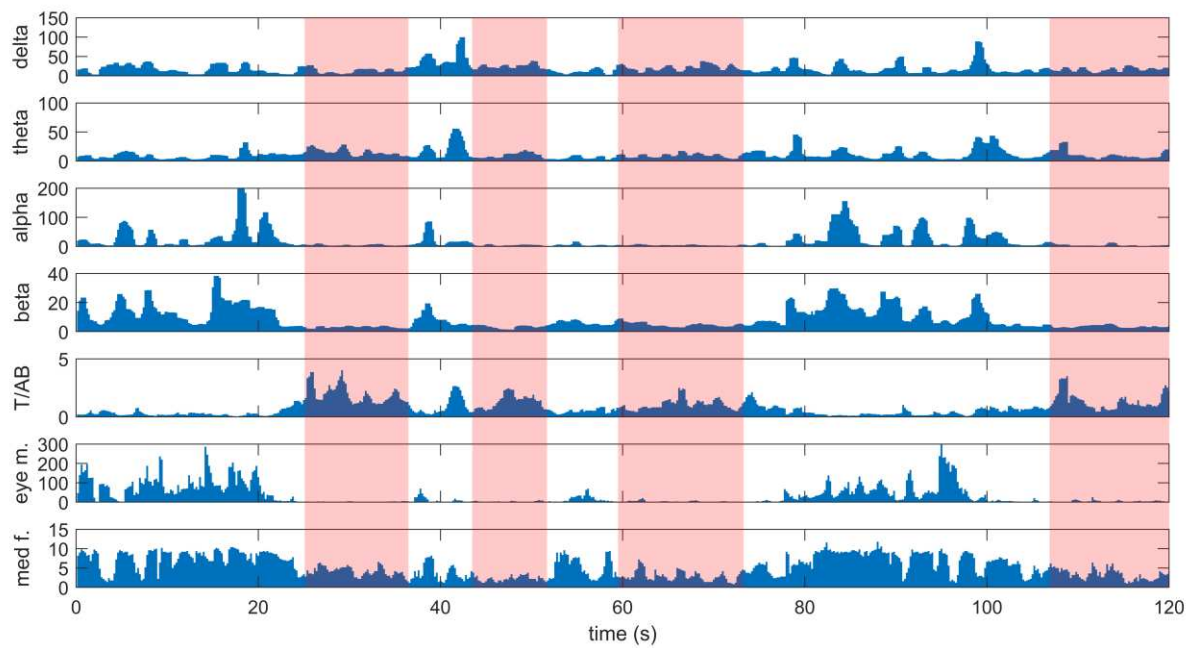


Figure 3. The occurrence of a microsleep episode (MSE, ○), AASM defined sleep onset (■), and if no sleep occurred the end of the Maintenance of Wakefulness Test (▲), i.e. set to 40 min, are indicated. Each horizontal line on the y-axis (scaled in percentage to the number of patients) represents one out of the 42 patients with at least one MSE. (a) Zero on the x-axis represents lights off, and patients are sorted according to the sleep latency (AASM-SL). (b) Zero on the lower x-axis corresponds to the occurrence of the first MSE, and the following MSEs and sleep onset are plotted relative to this time point. Patients are sorted according to the interval between the first MSE and sleep onset. The blue bars on the right indicate the cumulative MSE duration relative to the interval between the first MSE and sleep onset (upper x-axis in %), and illustrate a tendency towards a higher relative cumulative MSE duration in case of shorter first MSE to sleep onset intervals.

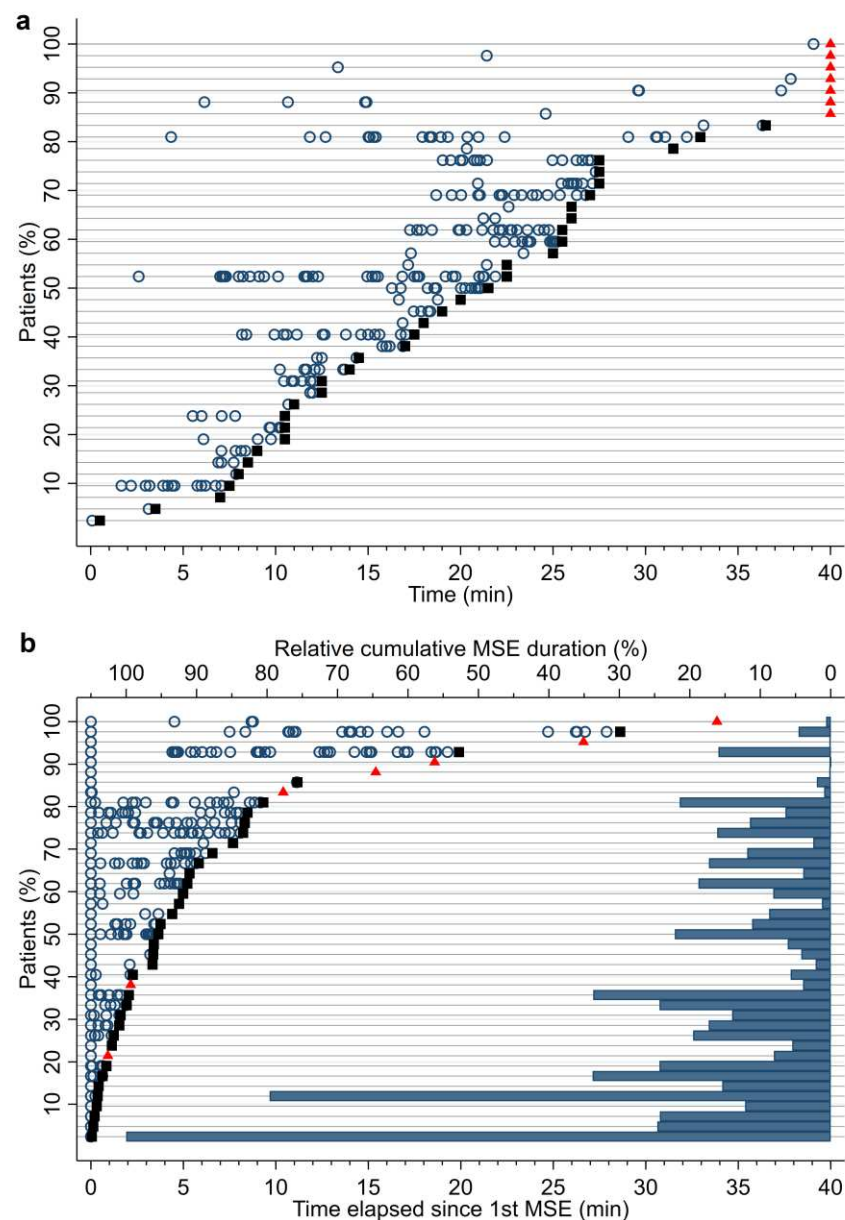


Figure 4. Characterisation of the 245 microsleep episodes (MSEs) scored in the 42 patients with at least one MSE preceding sleep (AASM defined). In three patients, continuously scored sleep (“MSE > 15 s”) was preceding AASM defined sleep, and therefore included in this analysis. The subfigures illustrate the frequency distributions of (a) the median MSE duration in a patient, (b) the duration of all scored MSEs, (c) the cumulative MSE duration of patients, (d) the total number of MSEs occurring in a patient, and (e) inter-MSE intervals, whereas the interval between lights off and the first MSE was excluded, and the interval between the last MSE (prior to sleep) and sleep was included (if ≥ 1 s; exclusion: $n = 11$).

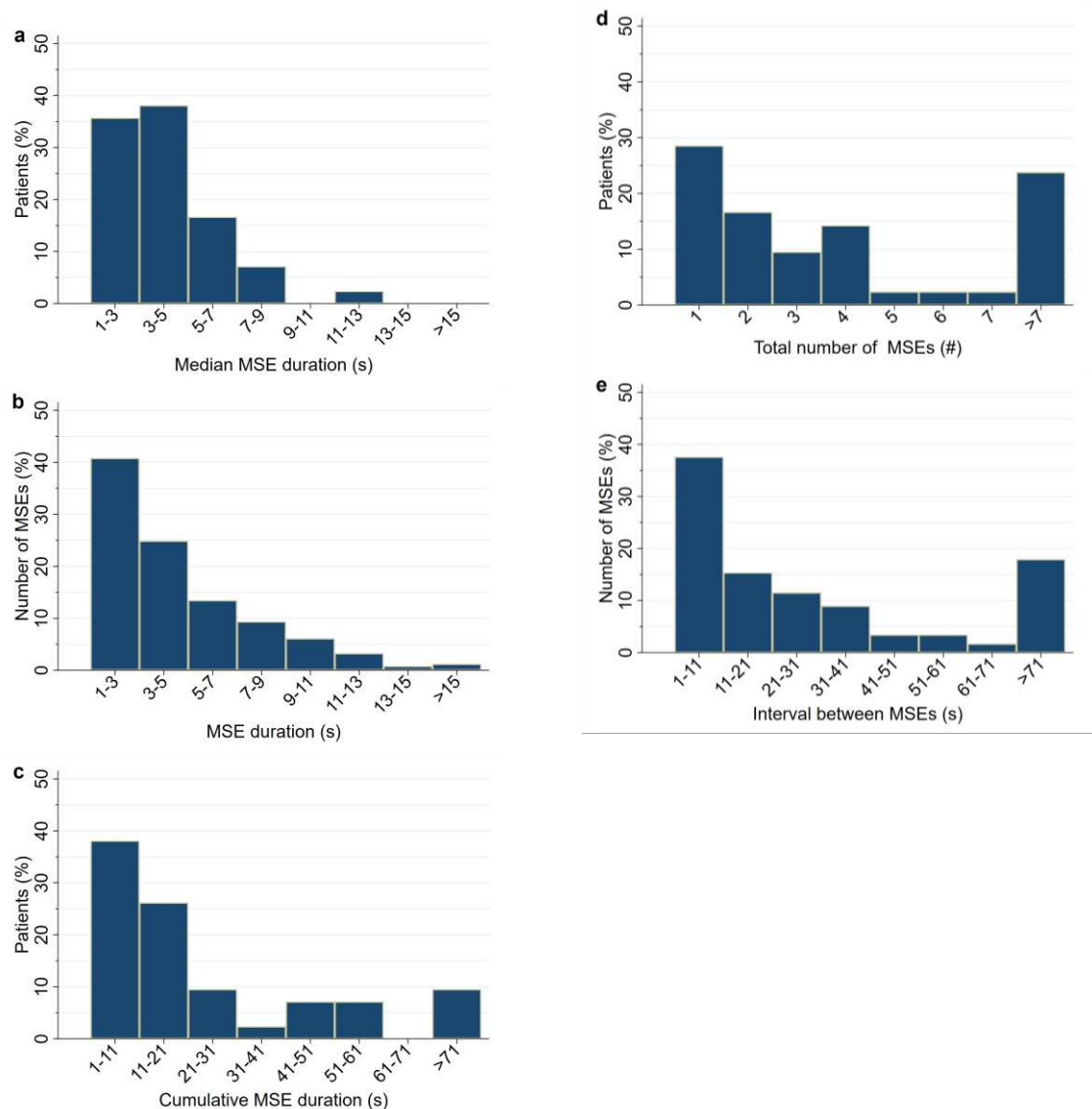


Figure 5. The AASM defined sleep latency (AASM-SL) as a function of the latency to the first microsleep episode (MSE-L) is illustrated for the patients with at least one MSE prior to sleep ($n = 42$). The seven patients that did not reach sleep (AASM-SL = 40 min), were excluded for the linear regression (red line). The grey 45° line indicates equal latencies for MSE-L and AASM-SL, while all data points above this line indicate that the MSE-L was shorter than the AASM-SL.

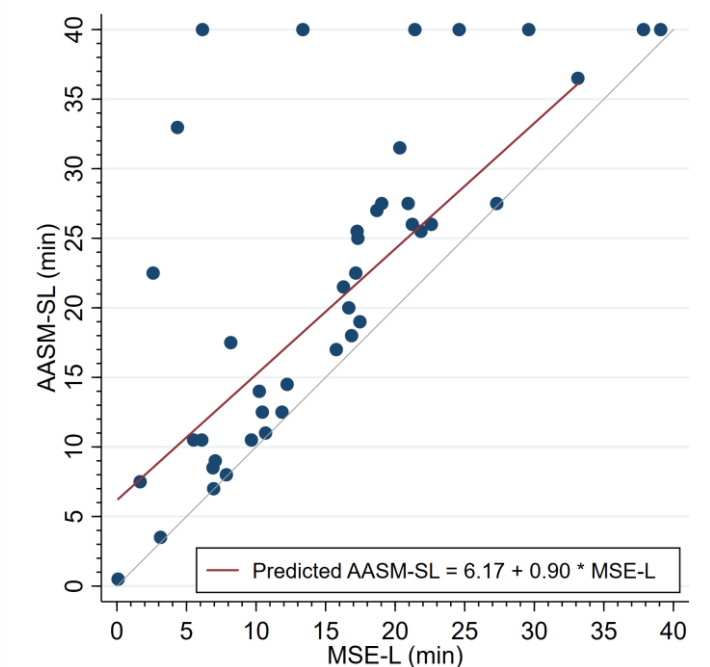
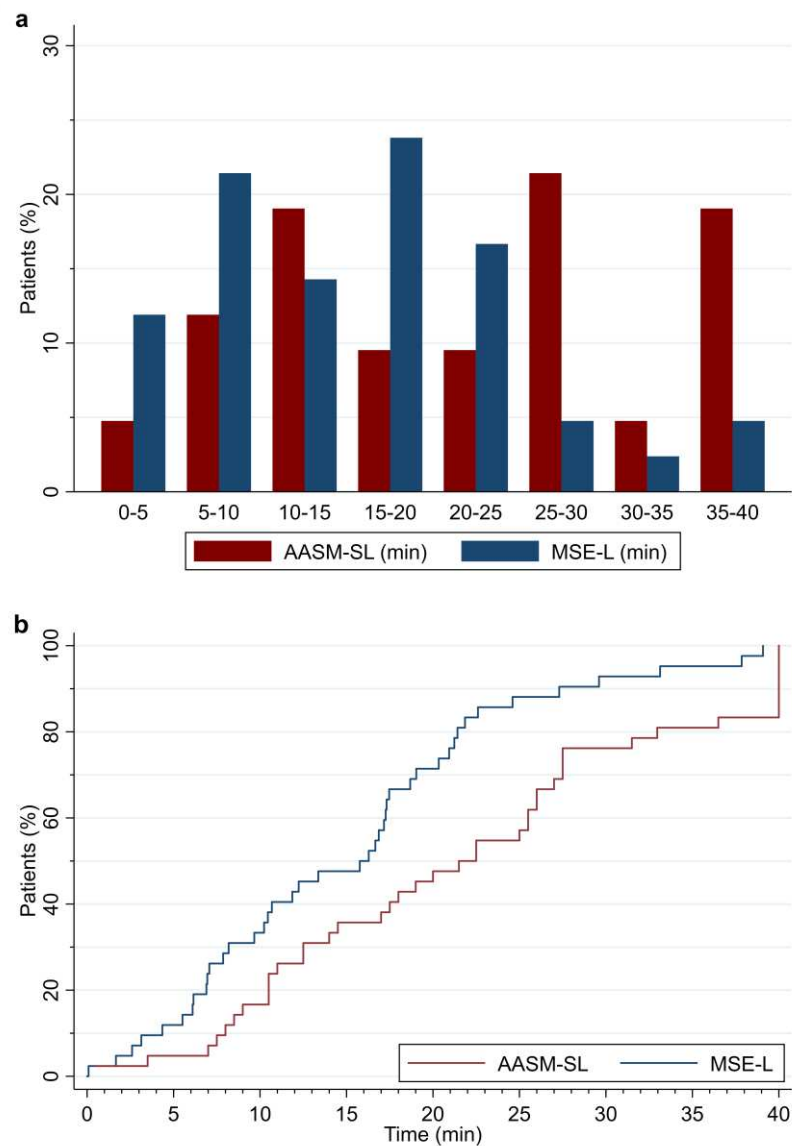


Figure 6. The latency to AASM defined sleep (AASM-SL, red) and to the first microsleep episode (MSE-L, blue) of the patients with at least one MSE prior to sleep ($n = 42$) are illustrated. (a) Shows the distribution of the latencies in 5-min intervals, with a majority of MSEs occurring in the first 25 min. The AASM-SL peaks at 25-30 min and the high incidence in the 35-40 min bin was due to AASM-SL which was set to 40 min when no sleep occurred. (b) Depicts the corresponding Kaplan-Meier curves of the occurrence of the first MSE or sleep.



Tables

Table 1. Bern continuous and high-resolution wake-sleep (BERN) scoring criteria.

Microsleep episode (MSE)	<p><i>Localisation:</i> ≥ 1 occipital channel (O1-M2, O2-M1)</p> <p><i>Duration:</i> 1 - 15 s *</p> <p><i>Mandatory features:</i> Predominant, mostly irregular and polymorphic theta activity with (I) slowing of > 1 Hz in case of slow background activity or low-voltage EEG, (II) in comparison to full wakefulness poorly delimited or absent alpha activity, with a simultaneous drop in beta activity, and (III) eyes ≥ 80 % closed (visually estimated in face videography).</p> <p><i>Optional features:</i> Slow eye movements typically precede and persist throughout a MSE. Loss of muscle tone (e.g. dropping of the head) can be observed.</p> <p><i>Additional scoring criteria (mandatory):</i></p> <ul style="list-style-type: none"> - If the MSE occurs in both occipital channels, it shall be scored as “bilateral MSE” and if the MSE occurs only in one occipital channel, it shall be scored as “unilateral MSE”. - If a MSE is interrupted by clear alpha-activity/alpha-spindle of a duration of ≥ 1 s, the MSE must be terminated and a new MSE shall be scored after the interruption. If a MSE, for example, starts bilaterally and is unilaterally interrupted with alpha-activity, the scoring of the bilateral MSE shall be stopped and continued as unilateral MSE in the corresponding derivation. <p>* in the rare case of continuous sleep > 15 s and without fulfilling the AASM criteria for sleep due to being spread over two consecutive epochs, this BERN type of “sleep” was treated as a “MSE > 15 s”.</p>
Microsleep episode candidate (MSEc)	<p><i>Localisation:</i> ≥ 1 occipital channel (O1-M2, O2-M1)</p> <p><i>Duration:</i> 1 - 15 s</p> <p><i>Mandatory features:</i> High likelihood of, with similar features as for, but not fulfilling all criteria of a MSE.</p> <p><i>Additional scoring criteria (mandatory):</i></p> <ul style="list-style-type: none"> - If a MSEc is interrupted by clear alpha-activity/alpha-spindle of a duration of ≥ 1 s, the MSEc must be terminated and a new MSEc scored after the interruption. - In contrast to a MSE, a MSEc is not scored as uni- or bilateral. - If a MSEc cannot be clearly delimited, it shall be scored as an episode of drowsiness or wakefulness.
Episode of drowsiness (ED)	<p><i>Localisation:</i> ≥ 1 occipital channel (O1-M2, O2-M1)</p> <p><i>Duration:</i> 1 - 30 s</p> <p><i>Mandatory features:</i> ED has distinct borders but the mixed frequency periods with acceleration and slowing within ED are without distinct borders. In addition, ED is also characterised by alternating between more regular and irregular activity and morphology of the EEG.</p> <p><i>Additional scoring criteria (mandatory):</i></p> <ul style="list-style-type: none"> - ED should be scored if the criteria for a MSE or MSEc are not fulfilled, and the episode does not resemble wakefulness.

Definition of the Bern continuous and high-resolution wake-sleep (BERN) scoring criteria. The BERN scoring criteria are applicable for AASM defined epochs of wakefulness.

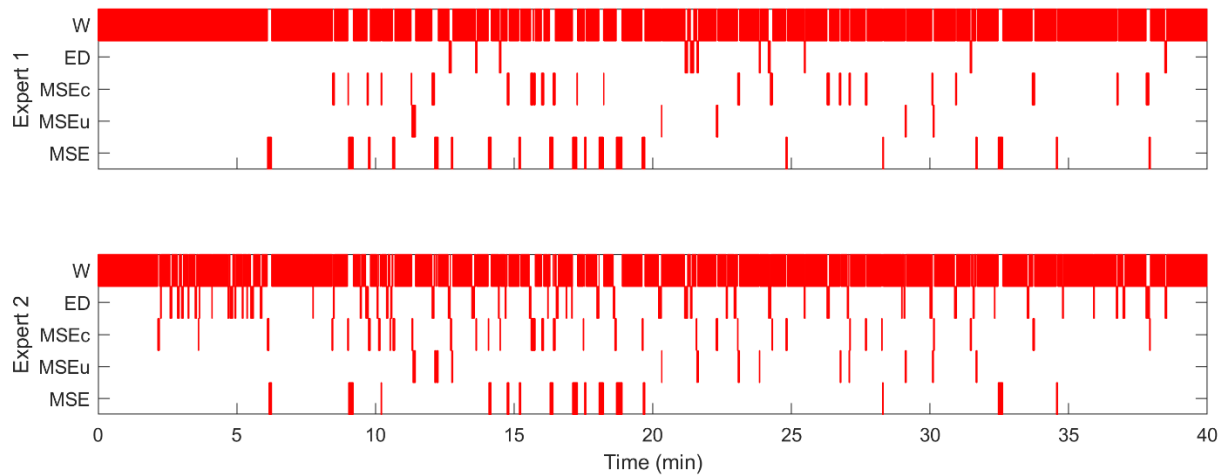
Table 2. Descriptive characteristics of microsleep episodes. Descriptive characteristics of microsleep episodes (MSEs) for the 42 patients with at least one MSE analysed until sleep (AASM defined). The latency to the first MSE (MSE-L) and the latency to sleep (AASM-SL) significantly differed ($z = 5.645$, $p < 0.0001$) but showed a strong positive correlation ($r = 0.7713$, $p < 0.0005$, $n = 35$). Median and boundaries for the interquartile range are reported. (*) Median of the median MSE duration per patient is reported. In three patients, continuously scored sleep (“MSE > 15 s”) preceded AASM defined sleep. (**) Calculated overall, not per patient; $n = 234$, after excluding 11 intervals between last MSE and sleep due to being shorter than one second.

Descriptive characteristics of microsleep episodes	
AASM-SL (min)	22.00 [11.00 – 27.50]
MSE-L (min)	16.02 [7.07 – 20.93]
Interval between 1st MSE and sleep (min)	3.71 [1.23-8.32]
Total number of MSEs (#)	3 [1 - 7]
Median MSE duration (s)*	3.5 [2.6 – 5.1]
Cumulative MSE duration (s)	13.1 [4.3 – 32.6]
Inter-MSE interval (s)**	19.7 [6.8 – 46]

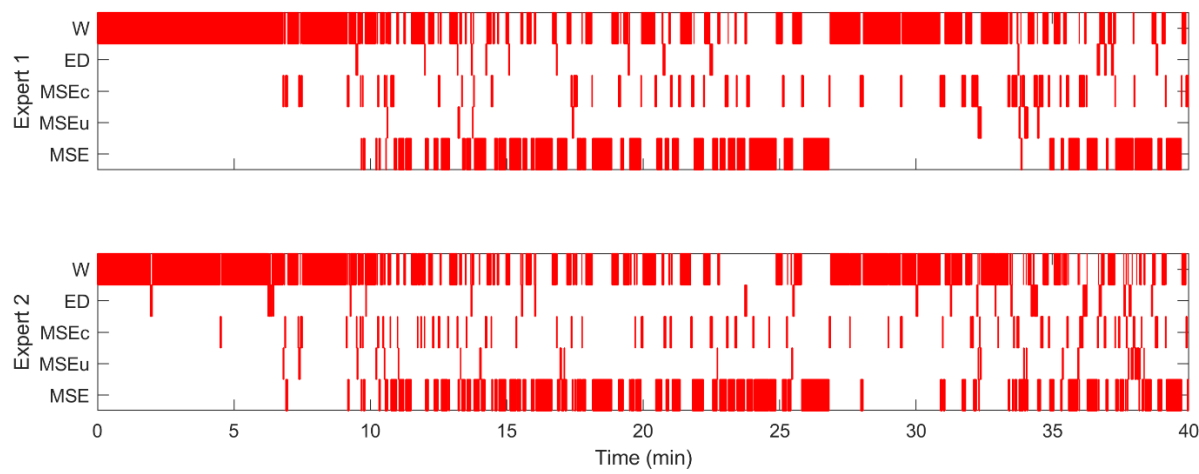
Supplementary material

Figure S1 (a-e). For each of the five patients selected for the inter-scorer comparison, the scorings of expert 1 (top) and expert 2 (bottom) are illustrated. The x-axis represents the time within the trial with zero indicating lights off. The y-axis shows the different categories: wakefulness (W), episode of drowsiness (ED), microsleep episode candidate (MSEc), unilateral microsleep episode (MSEu), bilateral microsleep episode (MSE) including continuously scored sleep (“MSE > 15 s”).

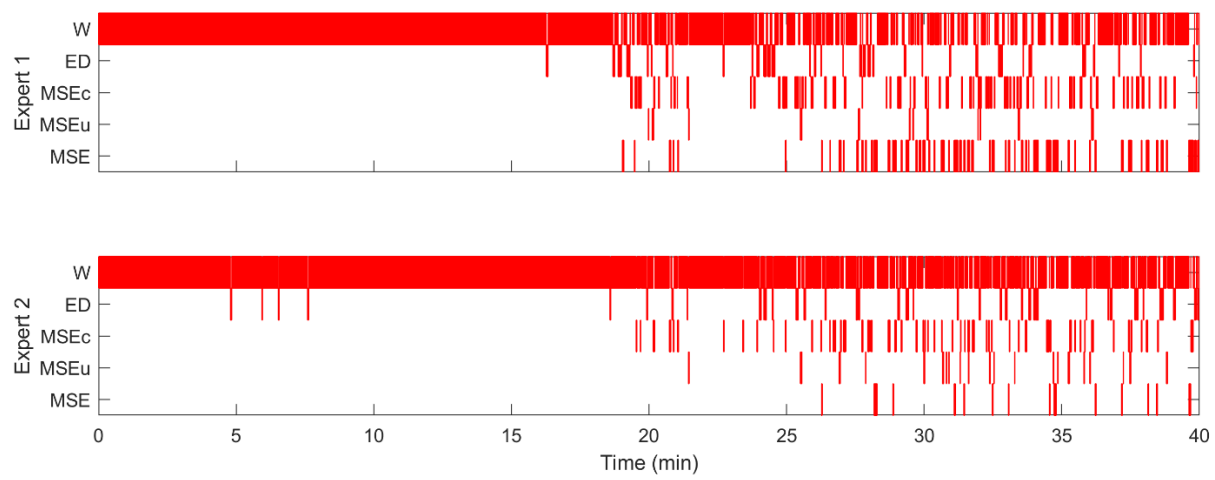
a. Patient 1: 3P0D.



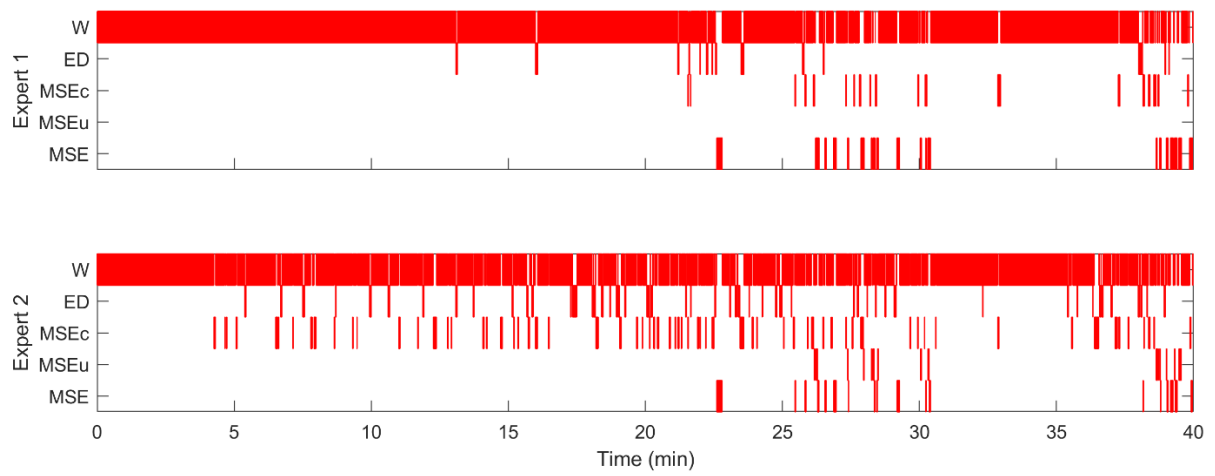
b. Patient 2: BSvO.



c. Patient 3: csxQ.



d. Patient 4: ibbz.



e. Patient 5: IhpU.

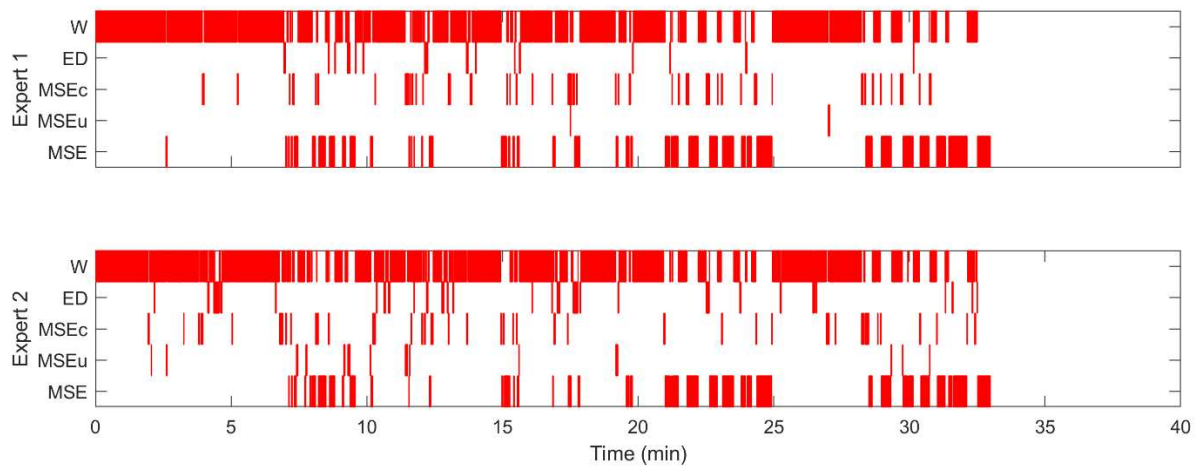


Table S1. The table represents the inter-scorer reliability of two independent experts for five patients. Overall performance measures across all patients (grey-shaded cells; pooled data of all patients) and mean and standard error of the mean across patients (white-shaded cells). The calculations are based on a binary classification system with two categories: positives and negatives, with a 200-ms resolution. The first category is reported in the first column (all events in the category are treated as the same type of event), the second category contains everything but the first category. The categories consisted of: bilateral (b), microsleep episodes (MSEs), unilateral MSEs (u), microsleep episode candidates (MSEc), episodes of drowsiness (ED), and wakefulness. For each combination, the following performance measures are reported: sensitivity, specificity, precision, accuracy, and Cohen's kappa coefficient (see Skorucak et al.²⁷ for the definitions of the performance measures).

1st Category	Sensitivity (%)	Specificity (%)	Precision (%)	Accuracy (%)	Kappa
MSEs(b)	74.1	98.1	86.6	94.7	0.77
	62.6 ± 12.7	97.7 ± 1.6	91.1 ± 2.8	94.7 ± 1.5	0.67 ± 0.10
MSEs(b,u)	80.4	97.8	86.5	95.2	0.81
	73.7 ± 11.2	97.4 ± 1.6	88.6 ± 2.1	95.1 ± 1.4	0.75 ± 0.08
MSEs(b,u) + MSEc	78.4	95.8	83.3	92.1	0.76
	74.2 ± 8.8	95.7 ± 1.2	78.5 ± 9.0	92.1 ± 1.3	0.69 ± 0.08
MSEs(b,u) + MSEc + ED	80.1	91.7	75.0	88.9	0.70
	77.8 ± 7.9	91.8 ± 1.7	70.1 ± 10.3	88.9 ± 1.4	0.64 ± 0.08
MSEc	23.3	95.3	24.1	91.0	0.19
	25.4 ± 3.7	95.3 ± 0.7	24.9 ± 4.9	91.0 ± 1.2	0.19 ± 0.04
ED	16.6	94.8	8.1	92.6	0.08
	18.2 ± 6.9	94.8 ± 0.7	7.4 ± 2.0	92.7 ± 0.6	0.07 ± 0.02